Therapeutic Utilization of the Diurnal Variation in Pituitary-Adrenocortical Activity

EUGENE J. SEGRE, M.D., AND EDWARD L. KLAIBER, M.D., *Palo Alto*

■ *The degree of pituitary-adrenocortical suppression resulting from exogenous corticosteroid is related to the time of day the steroid is administered. Morning administration has less effect and evening administration a greater effect than do divided doses given over the course of the day.*

Clinical studies have shown that in the great majority of patients with corticosteroid responsive diseases, an intermittent dosage schedule is at least as effective as is administration of an equal dose in a three or four times a day regimen. Other undesirable side effects of corticosteroid therapy may also be decreased by an intermittent schedule. It is suggested that the customary divided dosage schedule for corticosteroid administration be replaced with an intermittent regimen, the medication being given in the morning. This may be once a day, or, if therapeutic results are satisfactory, once every other day.

RECENT REPORTS have indicated that intermittent therapy with corticosteroids has less suppressive effect on the pituitary-adrenocortical axis than does the administration of the same amount of steroid in divided doses over the day. As part of our investigation of different regimens of corticosteroid administration, we have studied the dynamics of this pituitary sparing.

Material and Methods

Flumethasone,* a newly developed glucocorticoid of high potency, was administered to three normal male volunteers as a single daily dose of 0.75 mg. This dose was selected because previous experiments had shown that 0.75 mg, given in divided doses over the 24-hour period, would result in a mean 50 per cent suppression in urinary 17-hydroxycorticosteroid (17-OHCS) excretion.

In each therapy period flumethasone was administered orally for four days at one of three times: 8 a.m., 4 p.m. or midnight. Courses of therapy were random; they were separated by at least one week without treatment. During each therapy cycle, 24-hour urine collections were made on the two days preceding flumethasone administration and on the last two days of therapy.

Urinary 17-OHCS excretion was determined by the method of Silber and Porter.[11] Creatinine determinations were concurrently performed to assure completeness of the collections.

Results

The results are presented in Table 1. The mean excretion of 17-OHCS on the two days immediately preceding treatment is compared with the mean excretion on the last two of the four days of flu-

From the Institute of Clinical Medicine, Syntex Research, Palo Alto (Segre), and the Worcester State Hospital, Worcester, Mass. (Klaiber).

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*Flumethasone (6α,9α-difluoro-16α-methyl-11β,17α,21-trihydroxy-$\Delta^{1,4}$-pregnadiene-3,20-dione).

methasone administration. The results are expressed as per cent suppression. A trend is apparent. Administration of flumethasone at 8 a.m. resulted in a 40 per cent decrease in 17-OHCS excretion over the ensuing 24 hours, administration at 4 p.m. in a 61 per cent decrease, and administration at midnight in an 83 per cent decrease. The difference between the suppression resulting from a single dose at 8 a.m. and at midnight is significant at $P < .01$ level of confidence as determined by Student's t test. These observations may also be compared to the mean 50 per cent suppression when the same dose of flumethasone was administered in divided doses to another group of normal subjects.

Discussion

DiRaimondo and Forsham[2] suggested some years ago that 10 mg of prednisone administered at 8 a.m. caused less suppression of adrenocortical activity than did 2.5 mg administered every six hours around the clock. While this manuscript was in preparation Nichols and coworkers[7] reported that 0.5 mg of dexamethasone caused only partial suppression of cortisol secretion when administered at 8 a.m. or 4 p.m., but virtually complete suppression for a full 24-hour period when administered at midnight. Martin and Hellman[6] reported that the response to methopyrapone is also greatest in the hours immediately after midnight. Methopyrapone response is dependent on the sensitivity of the hypothalamus to decreased concentrations of circulating corticosteroid. It would appear that the response to feedback stimuli is temporally concentrated in the early morning hours when the diurnal burst of adrenocorticotropin (ACTH) secretion normally occurs. Neither an increase nor a decrease in circulating corticoid concentration at other times of the day has much effect.

The therapeutic implications with regard to maintenance of normal reactivity of the hypothalamic-pituitary-adrenal axis are obvious. Administration of glucocorticoids in the treatment of corticosteroid responsive conditions should be early in the morning, so that when the pituitary is ready for its next diurnal surge of ACTH secretion the administered corticosteroid will no longer be circulating in concentrations high enough to block it. The actual concentration still circulating at any time after administration will depend on several factors, including the biological half-life of the steroid and the size of the dose administered. Any investigation of the pituitary suppression resulting from different corticosteroid regimens must take these variables into consideration. If very large doses are therapeutically required, or if the duration of action of the steroid is especially prolonged, as appears to be true of some of the synthetic fluorinated corticosteroids, the pituitary suppressing activity of the exogenous corticoid may persist for 24 hours or longer. An every-other-day regimen of administration as suggested by Harter and coworkers,[5] or another intermittent schedule such as three to five successive days of each week may be required to permit pituitary escape. Morning administration would be less suppressive with these dosage regimens as well.

The application of these concepts to prevention of other undesirable side effects is less clear-cut. In the case of pituitary suppression, we are dealing with a peculiar diurnal variation in its sensitivity to feedback influences. If the same amount of exogenous glucocorticoid is needed to gain a given therapeutic goal with either once a day or divided dosage schedules, we are probably getting a net excess of administered corticoid in the once-a-day regimen, since in this situation the endogenous secretion will supplement the exogenous administration. The great variation in incidence of any

TABLE 1.—*Urinary 17-OHCS† (in mg per 24 hours) in Three Subjects Receiving the Same Dose of Flumethasone at Different Times of the Day*

Flumethasone 0.75 mg by mouth at	*Urinary Excretion of 17-OHCS in 24 Hours*								
	8 a.m.			*4 p.m.*			*Midnight*		
	Control	*Rx*	*Per Cent Decrease*	*Control*	*Rx*	*Per Cent Decrease*	*Control*	*Rx*	*Per Cent Decrease*
Subject A	9.7	4.5	46	12.5	2.9	77	9.4	2.2	77
Subject B	7.8	5.0	36	11.2	2.7	76	6.9	0*	100
Subject C	4.6	2.8	39	6.4	4.4	31	7.2	2.1	71
Mean ± SD	....	....	40 ± 5	....	....	61 ± 26	....	....	83 ± 15

*No Porter-Silber chromogen detectable.

†17-hydroxycorticosteroid.

Each control value represents the mean of determinations carried out on the two days immediately preceding treatment. Each Rx value represents the mean of determinations carried out on the third and fourth days of flumethasone administration.

particular corticosteroid side effect makes it difficult to establish whether intermittent therapy or the classical procedure of giving medication in divided doses three to four times daily results in fewer undesirable reactions. The available reports suggest that side effects such as peptic ulceration are less frequent if steroid treatment is given once daily or at less frequent intervals.[1,4,5,9,12] Prospective control studies in large populations are needed to establish this observation on a firm statistical basis.

Dougherty and coworkers[3] demonstrated that inflamed connective tissue concentrates administered cortisol with respect to blood and that the anti-inflammatory activity of cortisol continues to be exerted for a prolonged period after it has disappeared from the tissue. Persistence of the anti-inflammatory effect beyond the time when the anti-inflammatory agent can be measured in the inflamed tissue is not surprising. Many of the metabolic effects of the steroid hormones appear to represent the end result of a long chain of reactions triggered by an effect of steroid on nucleic acid synthesis.[10] The hormone has usually disappeared from the target tissues before changes in enzyme activities can be demonstrated. There is little reason to suspect that constant blood levels of corticosteroid are necessary for this triggering action.

An analysis of the therapeutic effectiveness of intermittent corticosteroid administration must consider the doses used and the duration of action of the individual corticosteroid employed. In general, the effectiveness of once a day therapy appears comparable to the conventional divided-dose regimens in the great majority of patients.[1,4,8] Indeed the same therapeutic end point may be reached with slightly smaller total doses.[4] Alternate day therapy has been effective in the treatment of asthma,[5] dermatologic disorders[9] and nephrosis,[12] but perhaps is not as effective in the treatment of adult rheumatoid arthritis.[8] This may be due to differences in dosage or in the steroids employed in the particular studies, or it may reflect a true difference in the response of the disease to corticosteroids.

Syntex Research, Institute of Clinical Medicine, Stanford Industrial Park, Palo Alto, Calif. (Segre).

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